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Do Positive Inotropic Agents Adversely Affect the Survival of Patients With Chronic Congestive Heart Failure?

I. Introduction

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No class of drugs for the treatment of congestive heart failure has generated as much passion as the oral inotropic agents. The first exciting reports that synthetic pharmacologic agents unrelated to digitalis or the catecholamines could stimulate cardiac contractility appeared in 1978 (1). These initial investigations (2) indicated that these new inotropic agents could produce dramatic short-term hemodynamic benefits in patients with advanced left ventricular dysfunction. Yet, 10 years have passed since the publication of these exciting findings, but thus far, no new orally active positive inotropic drug has been approved for the treatment of chronic congestive heart failure.

The available oral nonglycoside inotropic agents. It is of historic interest that the initial favorable reports of the effects of the new nonglycoside inotropic agents coincided with early studies of the hemodynamic effects of captopril in hypertension (3) and of teprotide in patients with severe left ventricular dysfunction (4), which suggested that converting enzyme inhibitors held promise for the treatment of congestive heart failure (4). During the next decade, however, the development of these two classes of drugs followed totally different courses (Fig. 1). The converting enzyme inhibitors have achieved widespread acceptance in the medical community in view of overwhelming evidence that these drugs can produce important short- and long-term hemodynamic and symptomatic benefits and can reduce the mortality of patients with chronic heart failure (5–8). In contrast, increasing doubts have been raised about the safety and efficacy of long-term therapy with the new positive inotropic agents, particularly those drugs that increase intracellular cyclic adenosine monophosphate (AMP) by inhibiting myocardial phosphodiesterase. Despite early promising results, the first phosphodiesterase inhibitor, amrinone, was withdrawn from clinical investigation because its unfavorable side effect profile prevented the administration of doses of the drug that were large enough to produce clinical improvement (9). The dramatic hemodynamic benefits of the imidazole derivatives (enoximone and piroximone) were accompanied by considerable gastrointestinal intolerance (10–12). The development of milrinone, a second generation bypyridine derivative, demonstrated that positive inotropic effects could be achieved with few adverse effects on the gastrointestinal tract (13,14), but the introduction of this agent coincided with a heightened awareness in the medical community that pharmacologic interventions could (and in fact, should) improve the survival of patients with congestive heart failure.

Do positive inotropic drugs influence survival in chronic heart failure? The first patients with heart failure to be treated with the new phosphodiesterase inhibitors had very severe heart failure; many had previously been unsuccessfully treated with vasodilators and converting enzyme inhibitors (14,15). The high mortality rate (14–17) of these patients should not have been surprising; nevertheless, it proved to be an enormous source of frustration for clinical investigators, who hoped that the impressive hemodynamic benefits seen after short-term treatment with amrinone and milrinone would be translated into prolonged clinical remission. When anecdotal experience suggested that patients who had benefited from treatment with these agents had an unexpectedly high mortality, concerns were raised regarding a potential deleterious effect of oral inotropic therapy. In the absence of a control group, however, it was difficult for any investigator to identify a direct adverse effect.

Nevertheless, the concerns of the cardiology community regarding the long-term consequences of positive inotropic therapy continued to grow. In part, these concerns were based on data from the experimental laboratory. All of the phosphodiesterase inhibitors appeared to act by increasing the intracellular level of cyclic AMP within the failing myocardium (18), but a high tissue concentration of this nucleotide was known to be toxic to the myocardium and had been implicated in the pathogenesis of experimental arrhythmias (19). Furthermore, long-term positive inotropic stimulation could be expected to increase energy expenditures in the failing heart and might thereby accelerate progression of the underlying disease. These theoretical fears were raised simultaneously with the publication of the first clinical report of amrinone (20).

These concerns about the long-term consequences of positive inotropic therapy were underscored by reports from the clinical laboratory. For example, in a number of uncontrolled studies, we (21) and others (22) noted that therapy with milrinone was associated with an increase in the frequency of ventricular arrhythmias. This observation raised

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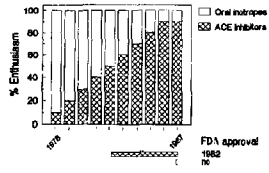

Figure 1. Schematic representing enthusiasm for either oral inotropic agents or angiotensin-converting enzyme (ACE) inhibitors as a portion of 100% enthusiasm. This demonstrates a progressively greater share of enthusiasm for ACE inhibitors, particularly since 1982, when efficacy data resulted in the approval of captopril by the Food and Drug Administration (FDA).

immediate fears, because high grade ventricular arrhythmias were known to be an independent determinant of mortality in patients with heart failure (23,24). This observation was coupled with reports (16,25) that suggested that long-term phosphodiesterase inhibition was accompanied by progression of the underlying disease, despite evidence for continued drug-related hemodynamic improvement. It was difficult, however, to be certain that these adverse hemodynamic and electrophysiologic effects were directly related to the administration of positive inotropic drugs rather than being a natural consequence of the severity of the disease.

Clinical studies that demonstrated that the phosphodiesterase inhibitors exerted direct vasodilating effects (26,27) have further heightened the controversy. These reports suggested that most of the hemodynamic actions of milrinone could be attributed to the drug's peripheral vasodilating effects. A few observers (28,29) even doubted whether this class of drugs could elicit a clinically relevant positive inotropic response in diseased segments of the myocardium, which are depleted of cyclic AMP. Yet, if the phosphodiesterase inhibitors act primarily as vasodilators, then these drugs should prolong life in patients with chronic heart failure, as do other vasodilators (8,30). However, a favorable effect on mortality has not been demonstrated with oral inotropic agents. Some investigators believe that such a beneficial effect is unlikely and suggest that the adverse myocardial and electrophysiologic actions of the inotropic drugs offset their favorable vasodilating actions. Uncontrolled studies appear to support this point of view (14,16,17,25).

There is little doubt that the continuing controversy about the effect of positive inotropic drugs on the survival of patients with chronic heart failure can only be resolved by the results of large scale, controlled, randomized clinical trials that are designed specifically to address this issue. Such trials have not yet been carried out, but new data are now available from small controlled studies that might provide some new insights into this controversial area. These recently completed studies are discussed in depth by Colucci and Packer in the following articles.

Is there a need for an orally active positive inotropic agent? Despite the dramatic benefits that generally accompany treatment with the converting enzyme inhibitors, many patients with chronic heart failure fail to respond favorably to these drugs or experience an adverse reaction that limits long-term therapy. The favorable effects of the converting enzyme inhibitors on mortality in chronic heart failure now permit patients to live longer but, as they do so, patients commonly reach a stage in their disease process when the magnitude of symptomatic improvement appears to be attenuated. Such patients represent the most critically ill patients and are frequently referred to centers specializing in heart failure research. Their increasing prevalence indicates that we have not achieved optimal therapeutic control of the heart failure process. It is in the context of this therapeutic void that orally active positive inotropic agents may provide some benefit.

It is not clear, however, that the new positive inotropic agents can fill this therapeutic void. Although the clinical utility of short-term intravenous positive inotropic therapy is well established in the management of acute heart failure or cardiogenic shock, there are few data that convincingly demonstrate the long-term efficacy of the phosphodiesterase inhibitors in chronic heart failure. The lack of such data should not yet be viewed with undue pessimism. The debate regarding the efficacy of digitalis has persisted for 2 centuries (31). It is only recently that compelling evidence has become available that demonstrates a favorable effect of digoxin in patients with chronic heart failure in normal sinus rhythm (32,33). Yet, a review of the early enthusiasm and subsequent disillusionment that followed the introduction of oral beta-adrenergic agonists should remind us that not all positive inotropic agents are destined to find a place in the management of chronic heart failure (34,35).

If the new phosphodiesterase inhibitors prove to be effective in the treatment of heart failure, what will be their role? These agents would appear to be desirable for the treatment of patients with the most severe symptoms, particularly those individuals who have been unsuccessfully treated with conventional vasodilators and converting enzyme inhibitors. On the other hand, if these drugs do not improve or actually shorten survival, their use will probably be relegated to the short-term circulatory support of patients awaiting cardiac transplantation.

Conclusions. The role of the new positive inotropic agents in the treatment of chronic heart failure remains undefined. In contrast to the development of converting enzyme inhibitors, that of the phosphodiesterase inhibitors has been marked by persistent concerns about their efficacy and safety. More clear-cut evidence of efficacy and safety will be required; if such evidence is not forthcoming, this

class of drug will probably never be approved for the treatment of chronic heart failure. It is not clear, however, that all future positive inotropic agents will be greeted by the skepticism that has accompanied the development of the phosphodiesterase inhibitors. It is possible that new approaches to the design of inotropic drugs (calcium sensitization, for example) can be developed on the basis of an evolving understanding of the cellular and biochemical abnormalities in heart failure. Such creative solutions may lead to important therapeutic advances.

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